PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kasid et al.

Art Unit: 1635

Application No. 09/930,283

Examiner: T. Gibbs

Filed: August 16, 2001

For: LIPOSOMES CONTAINING OLIGONUCLEOTIDES

AMENDMENTS IN RESPONSE TO OFFICE ACTION DATED OCTOBER 23, 2002

Amendments to the specification:

First paragraph on page 2, beginning at line 1:

Summary of the Invention:

It is possible to radiosensitize tumor cells by administration of compositions containing the Human antisense c-*raf*-1 oligodeoxyribonucleotide (ODN/oligo) sequence: 5' -GTGCTCCATTGATGC- 3' (SEQ ID NO: 1) wherein only the end bases are phosphorylated is a preferred sequence. Antisense sequences of up to 40 bases which containing this sequence may be used in accord with the teachings of this disclosure. A composition of the 25-mer oligo:
5' –CCTGTATGTGCTCCATTGATGCAGC- 3' (SEQ ID NO: 2) wherein the sequence is also effective. Compositions comprising cationic liposomes containing at least one non-toxic cationic lipid, phosphatidylcholine and cholesterol may be used as a carrier system.

Second paragraph on page 2, beginning at line 14:

Description of the Invention:

The search for clinically useful radiation sensitizers for treatment of cancers which fail to respond to radiation therapy has been actively pursued. This invention provides specific sequences which, while inducing radiation sensitivity on tumor cells, is non-toxic to normal tissue. As little as 10 pmol/μl of the sequences encapsulated in liposomes is effective when tumor cells are contacted with the compositions. It was found that the expression and enzymatic activity of Raf-1 protein are inhibited in cells exposed to *raf* antisense oligodeoxyribonucleotide (As-ODNs) directed against the translation initiation site of human c-*raf*-1 cDNA. In contrast, treatment of cells with an equimolar concentration of *raf* sense oligodeoxyribonucleotide (S-ODNs) had no effect on the expression and activity of Raf-1. Furthermore, it was observed radiosensitization of raf As-ODNs-treated SQ-20B cells. The dose modifying factor of As-ODNs treatment was ~1.4. This demonstrates that *raf* As-ODNs is a DNA sequences-specific radiosensitizer which may have potential for use in the radiation therapy of cancers. Hence, the method of the invention comprises administration of a radiosensitizing effective amount of at least one antisense nucleotide of no more than 40 bases containing the sequence 5' -GTGCTCCATTGATGC- 3' (SEQ ID NO: 1).

Second paragraph on page 4, beginning at line 14:

Materials and methods

Oligodeoxyribonucleotides

The sense and antisense *raf* ODNs were designed against the translation initiation site of human c-*raf*-1 cDNA in accord with the teachings of Bonner (Bonner *et al.*, Nucleic Acids Res., 14:1009-1015, 1986), and have the following sequence: sense ODN (ATG_S *raf*), 5' -GCATCAATGGAGCAC- 3' (SEQ ID NO: 3); antisense ODN (ATG-AS *raf*), 5' -GTGCTCCATTGATGC- 3' (SEQ ID NO: 1), only two of the bases, one at each end, are phosphorothiated. While antisense sequences of raf of up to 40 bases containing SEQ ID NO: 1 may be used, the larger sequences may be less effective. The fully phosphorothioated sequences may also be effective, but are more likely to cause toxic effects. That the sequences having only the end bases phosphorothioated are non-toxic to normal cells greatly enhances the value of such sequences for use in targeting malignant cells.

Amendments to claims:

4. A composition of claim 3 wherein the antisense sequence is of the formula 5' –GTGCTCC[C]ATTGATGC- 3' (SEQ ID NO: 1) wherein only the terminal sequences are phosphorothioated.

9. A method of radiosensitizing tumor tissue by administration of a radiosensitizing effective amount of at least one antisense oligonucleotide of no more than 40 bases containing the sequence 5' -GTGCTCCATTGATGC- 3' (SEQ ID NO: 1).

11. [A method of claim 9 wherein the oligonucleotide is phosphorothioated at only the end nucleotides.]

15. A method of claim 9 wherein the oligonucleotide is of the formula 5' -GTGCTCCATTGATGC- 3' (SEQ ID NO: 1) and only the end bases [only] are phosphorothioated.

16. A composition of matter comprising liposomes containing the sequence 5' –GTGCTCCATTGATGC- 3' (SEQ ID NO: 1) in a pharmaceutically acceptable carrier.

26. A method of claim 18 wherein the oligonucleotide is administered directly to the target tissue.

27. A method of claim 18 wherein the oligonucleotide is administered into the arterial supply to the target tissue.